Remarks

Claims 1-7 are pending in the application. Claims 9-12 are designated herein as withdrawn pursuant to a restriction requirement. Applicants expressly reserve their right to file one or more divisional applications with respect to any of the non-elected subject matter.

Claim Rejections – 35 USC §103

The Examiner rejected Claims 1-7 under 35 U.S.C. §103(a) as being unpatentable over Ohsumi et. al. (U.S. Patent No. 6,815,428; Of record) in view of journal publication by Diez-Sampedro et al.

This Office Action is non-final due to the new/modified grounds of rejection.

The Examiner asserts the following:

> The Ohsumi '428 patent teaches pyrazole-O-glycoside derivatives represented by formulas (1A) and (1B) for use as a diabetic medicine (abstract; column 1, lines 55-67; column 2, lines 1-14; claim 1). Exemplary compounds 1-16 are also shown (columns 31-35). Pharmaceutical compositions comprising '428 compounds inhibit the Na+-dependent glucose transporter (SGLT), which reduces renal glucose reabsorption at renal uriniferous tubules (column 1, lines 15-18 and lines 37-40). As a result, the level of blood sugar decreases. SGLT-1 and SGLT-2 are known membrane proteins which transport glucose.
>
> The Ohsumi '428 patent does not teach pyrazole-O-glycoside derivatives wherein the C-4 hydroxyl is substituted with a fluorine atom.
>
> Diez-Sampedro et al. teach the effects of varying the hydroxyl groups on the glucose ring and its recognition by the Na+-dependent glucose transporter (SGLT1). SGLT1 is highly selective for its natural substrates, D-glucose and D-galactose (abstract). Diez-Sampedro et al. individually substituted the different hydroxyl groups on the glucose ring with a hydrogen, fluorine or methyl group and studied the ability of SGLT1 in recognizing and binding the modified substrate (p. 49189, column 1, subsection "Compounds"; p 49189, column 2, full paragraphs 3-5). The only increase in the apparent affinity, compared with glucose, was found when the equatorial hydroxyl group in the fourth position was replaced with a fluorine atom (4F4DOglc) where the K0.5=0.07mM (p. 49189, column 2, fifth full paragraph). Since 4F4DOglc had a lower K0.5 compared with glucose (six times higher affinity), Diez-Sampedro et al. concluded that the hydrogen bond donation of the fourth position of glucose was detrimental to sugar binding (p.49192, column 1, third full paragraph).

> It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the Ohsumi '428 patent, regarding pyrazole-O-glycoside derivatives that inhibit the Na+-dependent glucose transporter (SGLT) for use as a diabetic medicine, with the teachings of Diez-Sampedro et al., regarding the increased apparent affinity of 4F4DOglc by SGLT as compared with the native glucose substrate. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Diez-Sampedro et al., that SGLT has a higher apparent affinity for the glucose substrate when the 4-hydroxyl group is replaced with a fluorine atom. A medicinal chemist would view that a compound with an increased apparent affinity for a receptor, as in the situation described by Diez-Sampedro et al., can likely serve as an inhibitor of the substrate, and would thus have been motivated to synthesize such a compound as inhibitors of SGLT can be used as a diabetic medicine.
>
> Thus, the claimed invention as a whole is prima facie obvious over the combined teachings of the prior art.

Applicants respectfully disagreed with this rejection in the Response to the Office Action dated 13 April 2009. Applicants' arguments are set forth below.

Oshumi et al. discloses certain SGLT inhibitors. Oshumi further discloses (column 1, lines 9-18) the following:

> Na^+-dependent glucose transporter (SGLT) is a membrane protein which transports glucose, and SGLT-1 and SGLT-2 are known. SGLT-2 mainly expresses in renal uriferous tubules. Glucose that is filtered in glomeruli is reabsorbed at the renal uriferous tubules via SGLT, and the glucose taken is reused in the body through the bloodstream. When SGLT is inhibited, the amount of the glucose reabsorbed at renal uriniferous tubules lowers, and the glucose is discharged through urine. As a result, it is considered that the level of blood sugar decreases.

Oshumi makes no disclosure regarding SGLT-1 and SGLT-2 differentiation.

WO01/27128 (hereinafter, "Ellsworth et al.", cited on page 1, line 21, of the specification of the instant application) describes the SGLT2 transporter (page 2, line 11 to page 3, line 19) in some detail and states that "[i]nhibition of SGLT2 would be predicted to reduce plasma glucose levels via enhanced glucose excretion in diabetic patients" (page 3, lines 19-21).

Ellsworth et al. then discloses the following on page 3, line 22 to page 5, line 3:

> SGLT1, another Na-dependent glucose cotransporter that is 60%

identical to SGLT2 at the amino acid level, is expressed in the small intestine and in the more distal S3 segment of the renal proximal tubule. Despite their sequence similarities, human SGLT1 and SGLT2 are biochemically distinguishable. For SGLT1, the molar ratio of Na^+ to glucose transported is 2:1, whereas for SGLT2, the ratio is 1:1. The K_m for Na^+ is 32 and 250-300 , for SGLT1 and SGLT2, respectively K_m values for uptake of glucose and the nonmetabolizable glucose analog α-methyl-D-glucopyranoside (AMG) are similar for SGLT1 and SGLT2, i.e. 0.8 and 1.6 mM (glucose) and 0.4 and 1.6 mM (AMG) for SGLT1 and SGLT2 transporters, respectively. However, the two transporters do vary in their substrate specificities for sugars such as galactose, which is a substrate for SGLT1 only.

Administration of phlorizin, a specific inhibitor of SGLT activity, provided proof of concept in vivo by promoting glucose excretion, lowering fasting and fed plasma glucose, and promoting glucose utilization without hypoglycemic side effects in several diabetic rodent models and in one canine diabetes model. No adverse effects on plasma ion balance, renal function or renal morphology have been observed as a consequence of phlorizin treatment for as long as two weeks. In addition, no hypoglycemic or other adverse effects have been observed when phlorizin is administered to normal animals, despite the presence of glycosuria. Administration of an inhibitor of renal SGLTs for a 6-month period (Tanabe Seiyaku) was reported to improve fasting and fed plasma glucose, improve insulin secretion and utilization in obese NIDDM rat models, and offset the development of nephropathy and neuropathy in the absence of hypoglycemic or renal side effects.

Phlorizin itself is unattractive as an oral drug since it is a nonspecific SGLT1/SGLT2 inhibitor that is hydrolyzed in the gut to its aglycone phloretin, which is a potent inhibitor of facilitated glucose transport. Concurrent inhibition of facilitative glucose transporters (GLUTs) is undesirable since such inhibitors would be predicted to exacerbate peripheral insulin resistance as well as promote hypoglycemia in the CNS. Inhibition of SGLT1 could also have serious adverse consequences as is illustrated by the hereditary syndrome glucose/galactose malabsorption (GGM), in which mutations in the SGLT1 cotransporter result in impaired glucose uptake in the intestine, and life-threatening diarrhea and dehydration. The biochemical differences between SGLT2 and SGLT1, as well as the degree of sequence divergence between them, allow for identification of selective SGLT2 inhibitors.

Diez-Sampedro et al. teaches that 4-F-Deoxy-glucose has a strong affinity for the SGLT-1 receptor (Table 1, page 49190).

Applicants respectfully disagree with the Examiner's assertion that "[a] medicinal chemist would view that a compound with an increased apparent affinity for a receptor, as in the situation described by Diez-Sampedro et al., can likely serve as an inhibitor of the substrate, and would thus have been motivated to synthesize such a compound as

inhibitors of SGLT can be used as a diabetic medicine". On the contrary, Diez-Sampedro represents a "teaching away" inasmuch as it was known in the art (e.g. Ellsworth et al.) that inhibition of SGLT1 is undesireable due to predicted severe side effects.

The Examiner rejected this argument and stated that:

> This argument is not persuasive because Ellsworth et al. only teaches that "[i]nhibition of SGLT1 could also have serious adverse consequences". Thus, as Ellsworth et al. do not definitively teach that inhibition of SGLT would necessarily result in adverse consequences, it is considered that one of ordinary skill in the art familiar with the teachings of Ohsumi et al. and Diez-Sampedro et al. would be motivated to combine the teachings and replace the 4-OH group of the compounds disclosed by Ohsumi et al. with a fluoro group in order to increase its apparent affinity for SGLT, as suggested Diez-Sampedro et al., and thus produce a SGLT1 inhibitor that could be used as a diabetic medicine. Furthermore, Ellsworth et al., teach that the possible adverse consequences of inhibition of SGLT1 is a result of "mutations in the SGLT1 cotransporter," and do not teach that it is due to the direct inhibition of SGLT1. One of ordinary skill in the art is aware that receptor inhibition can result in different downstream effects depending on the structure of the compound and its mechanism of action. Thus, in the absence of any definitive teaching that inhibition of SGLT1 is detrimental, Ellsworth et al., would not necessarily "teach away" the combined teachings of Ohsumi et al. and Diez-Sampedro et al. Thus, the claimed invention as a whole is prima facie obvious over the combined teachings of the prior art.

Applicants respectfully assert that the Examiner has misapplied the standard for determining obviousness. A reference must be considered not only for what it expressly teaches, but also for what it fairly suggests, In re Burckel, 592 F. 2d 1175, 1179, 201 USPQ 67, 70 (CCPA 1979). There is no requirement that a reference *definitively* teach anything. Under the proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). A prior-art reference that diverges and points in a technical direction away from the present invention is evidence that the invention is unobvious. Prior art must be looked at in its entirety. The statement that "[i]nhibition of SGLT1 could also have serious adverse consequences as is illustrated by the hereditary syndrome glucose/galactose malabsorption (GGM), in which mutations in the SGLT1 cotransporter result in impaired glucose uptake in the intestine, and life-threatening diarrhea and dehydration" would suggest to one skilled in the art that a selective SGLT2 inhibitor would be desireable. Applicants assert that the claimed invention is nonobvious over the combined teachings of the prior art.

In view of the arguments herein, Applicants respectfully request that the rejection of Claims 1-7 be withdrawn.

Respectfully submitted,

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